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This project was designed to elaborate on possible effects of monochloroacetate (MCA), maleic acid (MA) and dichloromaleic acid (DCMA) on liver and kidney function. These studies have revealed important interactions between these test compounds and various known hepato- and nehphrotoxicants. Some of the interactions were of a potentiative nature and some were antagonistic. In addition, chromate appears to enhance the nephrotoxicity of some of these test compounds, an observation consistent with earlier reports on the interactions of chromate with other substances. All of the studies in this report suggest an important role in the tissue non-protein sulfhydryls.

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REPORT OF INVENTIONS AND SUBCONTRACTS

(Pursuant to "Patent Rights" Contract Clause) (See Instructions on Reverse Side.)

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b. TITLE Acting Vice Chancellor for Academic Affairs UNMC

c. I certify that the reporting party has procedures for prompt identification and timely disclosure of "Subject Inventions," that such procedures have been followed and that all "Subject Inventions" have been reported.

Paul J. Gardner — SIGNATURE OF AUTHORIZED CONTRACTOR/SUBCONTRACTOR OFFICIAL

1/3/91 — DATE (YYMMDD)

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Table of Contents

(a) List of Objectives

The overall objectives of this research effort were pursued exactly as presented in the original proposal. Since there were no changes in the objectives, they are only summarized below.

This research effort was designed to examine the effects of selected water pollutants and their interactions with chemicals known to produce liver or kidney damage. The water pollutants selected for study are known either to be ground or surface water contaminants or to be the by products of chlorination as used in the processing of drinking water. These test compounds were selected on the basis of their potential to produce effects on the kidney or liver based primarily on either preliminary experiments or chemical similarity to known toxicants.

The known nephrotoxicants or hepatotoxicants (standard or reference compound) were those well established with respect to site of action and for which much information exists with respect to mechanism of action.

Although where necessary it was the intent of this study to characterize the effects of water pollutants, the major thrust of the proposal was to examine the interactions of ground and drinking water pollutants with each other or in combination with substances known to produce effects on the kidney or liver. Hence, although useful information was obtained on the effects of substances such and dichloromaleic acid, the major effort was to examine the interaction of substances such as DCMA with other compounds. Experiments were designed to reveal either a potentiation or inhibition in the interaction studies.

The specific aims of the project were:

1. To examine the effects of certain drinking and ground water pollutants (monochloroacetate, dichloroacetate, dichloromaleate, etc.) on hepatic and renal function in dose-response studies with particular emphasis on low-dose and multiple-dosing protocols.

2. To examine the effects of selected drinking and ground water pollutants in conjunction with other drinking and ground water pollutants or with substances known to be nephrotoxic and/or hepatotoxic (e.g., mercuric chloride, chloroform, hexachlorobutadiene, maleic acid).

(b) Status of the Research Effort

Although not all of the aims of this proposal were realized during the three years of the study, major accomplishments were achieved. To date three manuscripts have been published and five more are in preparation or have been submitted for publication. Attached to this report (Appendix) are copies of the published papers (three) and copies of the manuscripts submitted or in preparation (five). Following are summaries of each of these projects.

Interactions of Maleic Acid and Dichloromaleic Acid

Although much is known about the effects of maleic acid on renal function, the dichloro analog, a known drinking water contaminant, had been little studied. Our studies demonstrated that dichloromaleic acid (DCMA) did indeed

have effects on renal function, although they were less dramatic than those previously reported for maleic acid. With acute dosing, DCMA produced anuric renal failure. In addition, and quite unsuspected, DCMA also appeared to alter hepatic function as judged by elevations of plasma ALT and AST concentrations. In addition, hepatic glutathione was reduced significantly by DCMA.

The more interesting observations, however, were obtained with the interaction studies of maleic acid and DCMA. Using doses of maleic acid and DCMA each of which were near threshold the combination produced dramatic results. First, it was clear that the female Sprague Dawley rat was much more sensitive to the combination of agents than the male. A clear potentiation of effects on the kidney were observed. This was evidenced both by an increase in urinary glucose excretion and a rise in the blood urea nitrogen (BUN). The male rat showed qualitatively similar responses, but these were quantitatively much less noteworthy. Although no mechanistic explanation is available for this interaction, it has been suggested that DCMA may alter the permeability of renal cells so that more maleic acid can enter and exert its effect on the kidney, that is, chromate exerts a non-specific disruption of membrane permeability. Studies to examine this point were not undertaken as part of this project.

Interaction of Dichloromaleic Acid and Carbon Tetrachloride

Carbon tetrachloride has long been studied as a model hepatotoxicant. Further, it has also been identified as a drinking water contaminant. In this interaction study, the dose of carbon tetrachloride selected was one that produced hepatotoxicity, but by no means a maximal effect. The dose of DCMA selected for the interaction studies was one which produced relatively dramatic effects on the kidney, but only modest effects on the liver.

Several interesting and potentially important interactions were observed. First, DCMA appeared to reduce the effects of carbon tetrachloride on the liver. This was particularly obvious when the "liver enzymes", ALT and AST, were measured in the plasma. The effects of the carbon tetrachloride alone were highly significant, and although DCMA alone had modest effects on these enzymes in the plasma, the combination of carbon tetrachloride and DCMA showed a dramatically reduced carbon tetrachloride response. This inhibition was statistically significant. Secondly, the combination of DCMA and carbon tetrachloride caused no reduction in hepatic glutathione. Carbon tetrachloride alone does not reduce hepatic glutathione, but DCMA alone does. The combination of agents yielded a hepatic glutathione concentration that was the same as control. Hence, with respect to the liver it would appear that DCMA blocks the ability of carbon tetrachloride to cause cell destruction and, hence, release of the "liver enzymes", while carbon tetrachloride appears to block the ability of DCMA to reduce hepatic glutathione. Although detailed mechanistic studies were not undertaken, it is possible that these effects result from the ability of these two compounds to interfere with the metabolism of each compound in the liver.

As indicated above, DCMA significantly elevated the BUN, an effect indicative of renal damage. In the Sprague Dawley rat, and at the dose employed, carbon tetrachloride had no such effect. However, the combination of carbon tetrachloride and DCMA significantly reduced the rise in BUN compared to that realized with DCMA alone. No mechanistic explanation is available for this interesting interaction.

Interaction of Potassium Dichromate and Maleic Acid

The PI had conducted a series of studies over several years to examine the effects of chromate as a potentiator of nephrotoxicity. Chromate had been found to potentiate the effects of mercuric chloride and citrinin (both known nephrotoxicants), i.e., the combination effect was greater than the sum of the individual effects. In all of these studies, chromate was employed in a subthreshold dose, i.e., the dose of chromate used revealed no effect on renal function. The plan of this investigation was to examine the effects of chromate pretreatment on the effects of DCMA and maleic acid on renal function in the rat.

Chromate was found to produce a dramatic increase in the effects of maleic acid on renal function. Maleic acid was used in a slightly larger than threshold dose, i.e., a dose which did produce effects on the kidney, but relatively modest effects. The dose of chromate used had no effect. The combination of agents produced a very dramatic rise in urinary glucose excretion, decrease in organic anion and cation uptake by renal slices, decrease in renal (but not hepatic) glutathione, and other parameters.

Since chromate is known to enhance the nephrotoxicity of a chemically-diverse group of substances (mercuric ion, hexachlorobutadiene, citrinin), it is possible that the effect of chromate is related to an ability of this ion in subthreshold doses to increase the permeability of proximal tubular cells to a variety of substances. Each of these are then able to exert an enhanced response on renal function.

Monochloroacetate Oral Toxicity and Depletion of Tissue Non-Protein Sulfhydryl Groups in Male and Female Rats

The goal of the first set of experiments was to determine the effects of orally administered monochloroacetate (MCA). MCA is a by-product of chlorination disinfection of water and is produced in the body as a metabolite of 1,1,2-trichloroethane, 1,2-dichloroethane and 1,1-dichloroethylene, chemicals widely used as degreasing agents and solvents, and frequent contaminants of groundwater. While the effects of the dichloro congener, dichloroacetate (DCA) are well studied, relatively little is known about MCA. Convulsions, and sometimes death have occurred several hours after poisoning of domestic livestock. In vitro, the reactivity of MCA for the sulfhydryl group of either GSH or cysteine is much less than that of iodo- or bromoacetate, likely due to differences in lability of the carbon-halogen bond.

In agreement with published reports, MCA caused fatal convulsions at high doses. Females were more sensitive than males, all survived 94 mg/kg but half the females died at 100 mg/kg whereas all the males survived at this dose, but not a higher (282 mg/kg) dose. Slight elevations of serum transaminase and urea nitrogen activities in the males receiving a higher dose (470 mg/kg) are suggestive of liver and kidney damage, however only one in four rats survived this dose.

Plasma lactate concentrations were decreased significantly after MCA, and plasma glucose concentration was also somewhat lower. These changes are opposite the results expected if MCA is similar to DCA in its effects.

MCA depletes renal and hepatic glutathione (GSH, measured as non-protein sulfhydryl activity, which is primarily GSH). The depletion is dose-related and time-dependent. Similar to agents that form GSH conjugates, MCA causes an initial decline in GSH, the extent of which is dose-related, which is followed by a rebound increase, as enzymes that synthesize GSH are activated and "overshoot" the normal value. Pretreatment of rats with the mixed function oxidase inhibitor SKF-525A did not block MCA's depletion of GSH. Therefore, it is likely that metabolism of MCA is not necessary for GSH conjugation. Since GSH functions as a "disposable nucleophile", protecting SH groups on proteins from being alkykated with various reactive metabolites produced within the cells, the effect of MCA on GSH is of concern if exposure to other chemicals occurs concurrently, as happens with contaminated drinking water sources.

Interaction of Monochloroacetate with Chloroform

Studies on the interaction of chloroform ($CHCl_3$) were initiated for several reasons. $CHCl_3$ is a model hepatotoxicant, widely used in studies of acute liver failure and in studying pathogenesis of chemically-induced liver failure. $CHCl_3$ is also nephrotoxic and has been used as a model nephrotoxicant monochloroacetate. (MCA) treatment was anticipated to increase $CHCl_3$ toxicity, as depletion of GSH increases $CHCl_3$ toxicity by allowing reactive metabolites, such as phosgene to react with essential tissue proteins. Assessing the interaction between MCA and $CHCl_3$ is of practical value, as MCA is a metabolite of common industrial solvents and $CHCl_3$ is an industrial solvent, furthermore both major by-products of chlorination disinfection of drinking water.

An interaction between MCA and $CHCl_3$ was shown for hepatotoxicity, but not nephrotoxicity, and the interaction was sex-specific. $CHCl_3$-induced hepatotoxicity, assessed as increases of plasma ALT, were increased 45-fold by MCA pretreatment in males, whereas in females, the changes were less pronounced (3-fold increase). Follow-up studies did show impaired hepatic function in the $CHCl_3$-treated animals, but still no interaction with MCA. Glomerular filtration was decreased in female rats, to about 60% control. This was associated with a slight elevation of blood urea nitrogen. $CHCl_3$ treatment alone also decreased glomerular filtration, but did not result in further impairment of renal function. Tubular function was assessed in both sexes as ability to accumulate organic ions by isolated tissue. There were no effects in females; in males MCA pretreatment appeared to protect the tissue from the effects of $CHCl_3$. MCA is a substrate for transport in the proximal tubule, so the protection may be related to substrate protection of the carrier.

Preliminary studies on the role of metabolism in the interaction between MCA and $CHCl_3$ suggest that both altered distribution of $CHCl_3$ as well as increased bioactivation contribute to the increase of toxicity. The ratio of protein bound $^{14}CHCl_3$ to total $^{14}CHCl_3$ was increased by pretreatment in both males (0.435 ± 0.014 vs. 0.299 ± 0.051) and females (0.677 ± 0.203 vs. 0.285 ± 0.006). The role of covalent binding needs additional study, however, as the MCA-pretreated females had greater binding to protein, compared to the MCA males (52 ± 14 vs. 26 ± 6) but much less toxicity.

Interaction Between Monochloroacetate and Hexachlorobutadiene or Carbon Tetrachloride

Conjugation with glutathione (GSH) is believed to be a step of bioactivation, rather than detoxication, for hexachlorobutadiene (HCBD), and depletion of GSH should decrease the formation of the toxic intermediate. Therefore, we expected monochloroacetate (MCA) pretreatment to decrease HCBD nephrotoxicity. MCA did not decrease HCBD nephrotoxicity, actually the magnitude of effect on the glomerular filtration indicator indicated that toxicity was greater in the MCA-pretreated groups. MCA pretreatment did protect the organic anion transport system from HCBD toxicity in males receiving the 200 mg/kg dose of HCBD. A similar effect was observed in males in the $CHCl_3$ study. We speculate that this protection is the result of increased substrate available and being bound to the transporter, preventing the transporter from being perturbed by the toxicant.

MCA greatly increased the hepatotoxicity of CCl_4, but only in the female rats. In males, there was a slight, and not significant increase in plasma ALT activity in the MCA pretreated groups, compared to saline controls. This is opposite of the results with $CHCl_3$, in which the males responded much more than females. Because of greater sensitivity to MCA lethality, the females receive a lower dose, and therefore have relatively more hepatic GSH at the time of CCl_4 administration. This suggests that the enhancement of CCl_4 hepatotoxicity is not related to MCA's ability to deplete hepatic GSH.

Interaction of Monochloracetate with Vinylidene Chloride

The initial studies on monochloroacetate (MCA) demonstrated that hepatic glutathione (GSH) is depleted by oral administration of MCA. This probably occurs as a result of conjugation of MCA, or its metabolites, with GSH, either directly or mediated by one or more of the GSH-S-transferase enzymes. GSH has many functions in the body; in the liver its role as a disposable nucleophile is particularly important. Free GSH in the cytosol interacts with electrophilic products of chemical metabolism, and the GSH-metabolite conjugate is then further metabolized and/or eliminated in the bile and urine. When GSH is not available, the reactive metabolites are able to interact with other, vital, proteins and lipids and such covalent interactions are believed to result in cell damage. Hepatotoxicity is greatly increased for compounds that form GSH conjugates with reactive intermediates when GSH is not available. Vinylidene chloride (VDC), or 1,1-dichloroethylene, is one such chemical.

VDC produces little toxicity when administered to animals with normal hepatic GSH content. However, VDC causes hepato- and nephrotoxicity if administered while hepatic is decreased, either through the normal diurnal cycle of GSH by fasting or by pretreating with a chemical that is highly conjugated with GSH, such as diethylmaleate (DEM). Therefore, it was hypothesized that MCA pretreatment would increase the hepatotoxicity of VDC.

In the initial experiments to test the hypothesis, VDC was administered 1 hr after MCA, as the previous experiments had shown that GSH was depleted at 1 hr. The dose of VDC, 200 mg/kg, was chosen to produce minimal toxicity in the GSH-replete group and substantial toxicity in the GSH-depleted rats, based upon published studies using oral administration (many of the studies of VDC used inhalation exposure). The results were surprising in that very little toxicity was observed in either VDC group, in either sex. Further

studies were done to confirm that an effect was not missed; liver excretory and kidney filtration and reabsorptive functions were measured using clearance techniques, as these are more sensitive indicators of organ dysfunction. While these studies did show that ability to excrete phenophthalein glucuronide in bile was more impaired by VDC in MCA-pretreated males, the effect was quite modest compared to increases of VDC toxicity reported for other techniques to lower hepatic GSH.

The next experiments were performed to ascertain that we could show increased VDC hepatotoxicity following GSH depletion with DEM; MCA pretreatment was also done. In those studies, DEM and MCA each dramatically increased VDC hepatotoxicity (plasma GPT increased from 304±2 SF units following GPT alone, 2100±475 after DEM pretreatment and 2356±645 after MCA pretreatment). With female rats, the effect of VDC was not as great (114±62 SF units/ml plasma) and was not as influenced by MCA pretreatment (536±252 for the MCA group, compared to 1177±44 for the DEM group).

The next series of studies were done to resolve the discrepancy between the two sets of experiments. One factor that was different was the size of the animals used. In the first study the males were smaller than in the second. Typically, one would expect lesser toxicity of a fat soluble compound in larger rats, as they typically have more fat that can serve as storage site, minimizing the exposure of other organs. Recent studies on pharmacokinetic modeling of VDC have shown that, with inhalation exposure, hepatotoxicity is greater in larger animals, as more VDC remains in the animal, compared to the smaller, leaner rats that are able to excrete the VDC across the lungs. The effect of size was compared directly. The effect of MCA on VDC-hepatotoxicity was greater in the larger males, compared to the smaller, and occured later in the larger rats.

The effect of size was not determined in the females, as little response was seen in either group. Rather, studies have focused on the role of mixed function oxidase system in VDC hepatotoxicity, in males and females. MCA treatment alone had a minor effect on cytochrome P450 content (approximate 15% reduction) or ethylmorphine deethylase, ethoxyresorufin O-dethylase and aniline hydroxylase. Future studies will compare the effects of MCA on gender-specific isozymes of cytochrome P450.

(c) Publications

The following manuscripts have been published.

(1) Alterations in the Renal Function of Male and Female Rats Exposed to Maleic Acid, Dichloromaleic Acid, and Both Compounds. Authors: W.R. Christenson, M.E. Davis and W.O. Berndt. Journal: Toxicology 56:229-238, 1989.

(2) Effect in the Rat of the Interaction of Dichloromaleic Acid and Carbon Tetrachloride on Renal and Hepatic Function. Authors: W.R. Christenson, M.E. Davis and W.O. Berndt. Journal: Fund. Appl. Toxicol. 13:493-499, 1989.

(3) The Effect of Combined Treatment with Potassium Dichromate and Maleic Acid on Renal Function in the Rat. Authors: W.R. Christenson, M.E. Davis, and W.O. Berndt. Journal: Toxicology Letters 49:21-27, 1989.

The following manuscripts are either in preparation or have been submitted for publication.

(1) Sex Differences in Monoclorolacetate Pretreatment Effects on Chloroform Toxicity in Rats. Authors: M.E. Davis and W.O. Berndt. Journal: Fund. Appl. Toxicol. (submitted).

(2) Effects of Monochloroacetate Pretreatment on Vinylidene Chloride Hepatotoxicity. Authors: J.B. Wijeweera, M.E. Davis and W.O.Berndt. Journal: In Preparation.

(3) Effects of Monochloroacetate on Glutathione and Vinylidene Chloride Toxicity. Authors: M.E. Davis, J.B. Wijeweera and W.O. Berndt. Journal: In Preparation.

(4) Monochloroacetate Pretreatment Increases Hexachlorobutadiene Nephrotoxicity. Authors: M.E. Davis and W.O. Berndt. Journal: In Preparation.

(5) Carbon Tetrachloride Hepatoxoxicity is Increased by Monochloracetate Pretreatment. Authors: M.E. Davis and W.O. Berndt. Journal: In Preparation.

(d) Professional Personnel

W.O. Berndt, Ph.D., Principal Investigator

M.E. Davis, Ph.D., Subcontractor

W.R. Christenson, Ph.D., Postdoctoral Research Associate

K. Johnson, B.S., Research Technologist

J.B. Wijeweera, Graduate Assistant

No advanced degrees have been awarded related to this project.

(e) Conclusions and Recommendations

These studies have demonstrated the potential inherent toxicity of several ground and/or drinking water pollutants. For example, dichloromaleic acid and monochloroacetate have been demonstrated to have a variety of effects. More importantly, however, was the demonstration of important interactions among the ground and drinking water pollutants and with various other nephrotoxic and hepatotoxic chemicals. For example, dichloromaleic acid potentiated the renal effects of maleic acid, while reducing the hepatotoxic effects of carbon tetrachloride. Monochloroacetate and chloroform demonstrated an interaction on hepatic function, but not on renal function. Furthermore, the interaction was sex specific. Also, monochloroacetate enhanced the magnitude of hexachlorobutadiene nephrotoxicity as indicated by glomerular function, and increased hepatotoxicity of carbon tetrachloride only in female rats.

The following recommendations are offered:

1) Mechanistic studies need to be undertaken to explain a number of the interactions.

2) Both mechanistic and descriptive studies are required to explain the sex differences observed with some of the ground and drinking water pollutants and for the sex specific interactions.

3) Long term, low dose studies should be conducted to assess possible interactions among the test compounds.